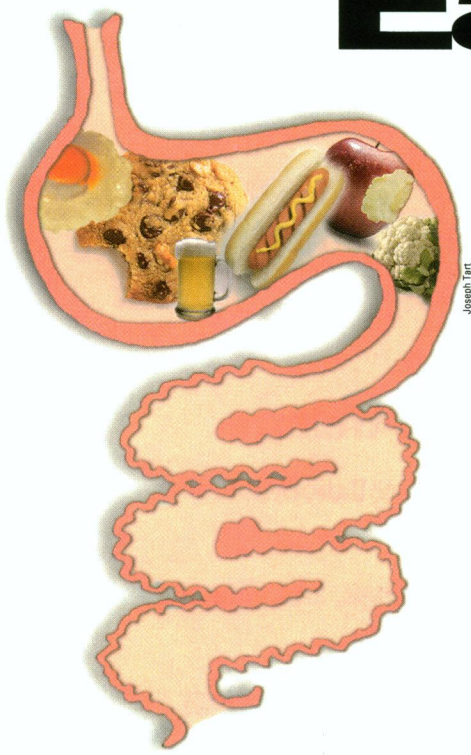
What's Eating Us about What We're Eating


Joseph Tart

Most people know the old adage: an appple a day keeps the doctor away. Increasingly, Americans are paying heed to the adage and taking it many steps further, eating their greens and downing their multivitamins in the hope of staving off all types of cancer. But the daily bombardment of conflicting advice about what to eat to stay healthy is enough to kill your appetite.

The connection between nutrition and cancer prevention is still controversial. The Food and Drug Administration will not allow labeling to the effect that food, food supplements, and vitamins prevent disease because it hasn't been proven. Almost all cancers of epithelial origin, such as prostate, colon, breast, and lung, are believed to be affected by diet, however, and scientists are struggling to pinpoint exactly how diet contributes to the development and progression of these cancers. In particular, researchers are investigating the contribution of fat and calories to a variety of cancers, including those outside the digestive tract, and the roles of fiber, nutrients, and antioxidant vitamins in cancer development. People are eager to hear the results of such research, hoping for a dietary prescription to prevent cancer.

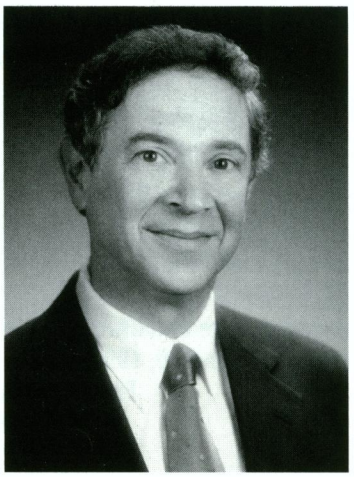
The growth of the National Cancer Institute's diet and cancer budget is evidence of the increasing interest in the diet–disease connection. Diet and cancer research began at NCI in 1974 with less than $3 million and grew by 1990 to more than $67 million. This funding was boosted by a series of scientific review reports, such as the one in 1980 by the National Research Council that suggested that many common human cancers, including cancers of the esophagus, stomach, liver, colon/rectum, lung, breast, and prostate are influenced by dietary patterns.

Follow-up reports by the U.S. Public Health Service and the National Research Council emphasized that further basic and applied nutritional research is needed, including clinical prevention trials. According to Peter Greenwald, director of the Division of Cancer Prevention and Control at NCI, the challenge that the agency and investigators face is huge: "to effectively translate diet and cancer information into a significant reduction of cancer incidence and mortality."

There is conflicting information about the precise role of dietary factors, and cause-and-effect relationships have not been established: for every confirmatory finding, another study finds no association. And many of the research questions are still fundamental; for example, when studying the contribution of fat in diet, should researchers really be looking at calories, since fat is so laden with calories? Most disturbing to some researchers is that in most cases the mechanisms behind diet and cancer have not been detailed. And the preliminary models that exist have been disputed.

Furthermore, there has been a reluctance to base recommendations for the modification of human diets on observations in experimental animals. Too often, some researchers say, laboratory animals are obese, so the contribution of nutrients to their health cannot be separated out.

"Teasing apart nutrition is a long row to hoe, and we have only just gotten started," said Bernard Weinstein, director of the Comprehensive Cancer Center at Columbia-Presbyterian Cancer Center. "With the thousands of compounds people put in their mouths, the study of diet is unbelievably complex."


NCI

Peter Greenwald—Translating diet information into cancer reduction is a huge task.

After years of study costing millions of dollars, NCI's Greenwald says that the knowledge at hand can suggest only general advice on how to cut your chances of getting cancer. "There is enough strong evidence to say that eating patterns affect your risk, not only of cancer, but of heart disease, and diabetes, and that you should cut your fat and stay trim," he said. "Although we have no answers yet on how specific constituents of food contribute to cancer, there are no studies that show you can be worse off by eating more vegetables and fruits."

Contradictory Evidence

Critical dietary factors implicated in the development of breast, colon, and other epithelial cancers consist of macronutrients, such as fat and fiber; micronutrients, such as vitamins and minerals; and the hundreds of non-nutritive constitutents in vegetables and fruits. For example, a diet rich in micronutrients found in fruits and vegetables appears to be protective for several types of cancer, including cancers of the lung, colon, rectum, bladder, oral cavity, stomach, cervix, and esophagus. Increased body weight is associated with postmenopausal breast and endometrial cancer. But the most vocal debates swirl around the contribution of fat in the diet for colon, rectum, breast, and prostate cancers.

This debate centers on the relative value of diet–disease associations depending on what type of study is done—epidemiological reviews, case–control studies, or randomized clinical trials. A major problem with most epidemiological studies is that they rely on the recall of the eater. Few randomized trials are conducted because they are expensive and difficult to manage. Problematic in all of these studies, researchers say, is the question of what other lifestyle factors may play a role. For example, a person who doesn't eat much fat is likely to eat more fruits and vegetables and be committed to other health measures such as exercise and reduced alcohol consumption. So the question remains: how can the separate effects of each of

these variables be determined?

Cancer researcher Cheryl Ritenbaugh of the University of Arizona says that in general such studies need to be more structured. Speaking at the Fourth International Conference on Prevention of Human Cancer, held in Tucson, Arizona, in June 1992, Ritenbaugh said: "There is a need for prospective, placebo-controlled clinical trials to test the low-fat, high-fiber, and increased numbers of fruit and vegetable servings hypothesis in specific high-risk populations for breast, colon, lung, and prostrate cancer."

Breast cancer. Breast cancer research may be the most contentious area of research and illustrates the difficulties in drawing connections between nutrition and malignancies. Greenwald summarizes the state of research on nutrition and breast cancer this way: "[Regarding] fat, there is a fair amount of agreement, but strong views the other way. Antioxidants are less clear, but need to be studied. Estrogen contribution is a hypothesis, but it is important. There are contradictory studies on pesticides. The contribution of exercise is debated. More study is needed on alcohol as a contributing factor."

The primary support for the proposed link between dietary fat and cancer is based on studies comparing countries such as Japan and China which have low fat intake and low rates of breast cancer, as well as cancers of the colon and prostrate, with countries such as the United States where fat intake is high and there are high rates of breast cancer. Similar correlations have also been observed in regions within countries, like Italy, in which the fat-consuming north has higher levels of breast cancer than the south, where the diet is leaner. But results of such epidemiological studies have different implications to researchers who question whether other variables may be responsible.

For example, scientists question whether low breast cancer rates in women in some countries are due not to eating less fat and its associated calories, which can trigger cell division, but due to having less body fat, a genetic factor contributing to cancer. Other researchers hypothesize that less fat consumption in childhood delays the onset of menstruation, and thus exposure to estrogen (prolonged estrogen exposure is considered a risk factor in breast cancer). Also, short stature has been positively correlated with low cancer rates in developing countries. Another factor to consider is that many rural populations have low breast cancer rates, where foods are often grown without harmful pesticides and residents may not be exposed to industrial contaminants or electromagnetic fields. Researchers are also studying the beneficial effects of fresh air and exercise in these populations, as well as lower alcohol consumption.

Some studies do seem to confirm the connection between fat and breast cancer. A 1990 meta-analysis of 12 case–control studies among postmenopausal women by the National Cancer Institute of Canada showed a 50% relative increase in breast cancer among women ingesting high intakes of saturated fat. Another analysis of postmenopausal women in Hawaii, by the Cancer Research Center of Hawaii, estimated that 10–20% of breast cancer could be prevented by significantly decreasing saturated fat intake.

Then a study appeared in October 1992 that rattled the accepted theories. The largest study of its kind, it offered convincing evidence that dietary fat and fiber do not play a role in breast cancer. Walter Willett and his colleagues at Brigham and Women's Hospital in Boston studied 89,494 women for 8 years, asking detailed questions about their diets and health. During the study period, 1,439 women developed breast cancer. But the researchers reported that no matter how they analyzed their data, they could not find any relationship between what the women ate and their chances of getting breast cancer. The fifth of women who ate the least fat, those for whom fat accounted for less than 25% of total calories, were just as likely to get cancer as the fifth of the women who ate the most fat, for whom fat accounted for more than 49% of their calories.

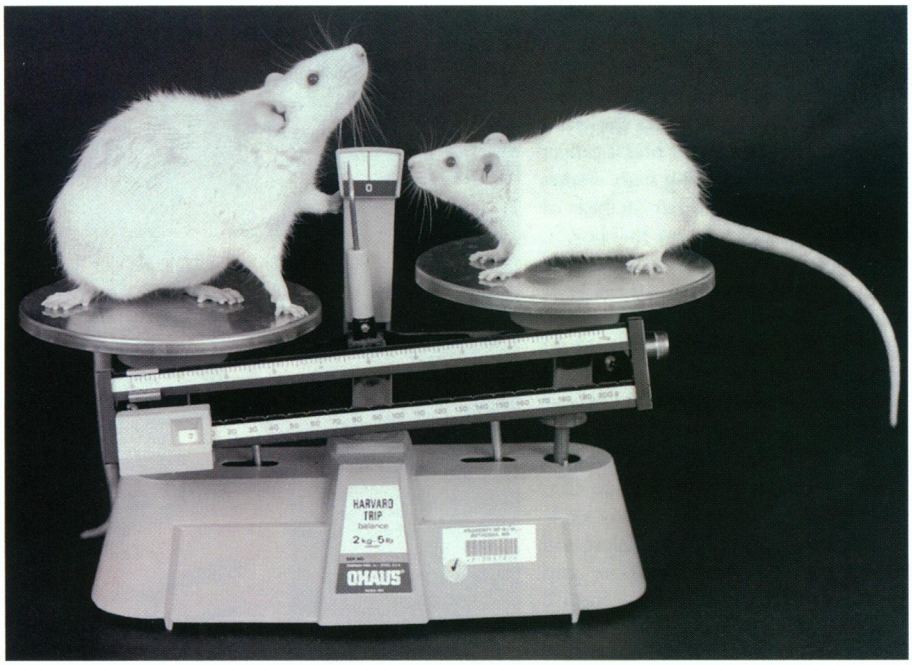
The fat factor. Researchers are now agreeing that fat plays a major role in many cancers but don't know precisely what that role is.

Criticism of Willett's study was intense and continues today because he claims no large study, epidemiological or randomized, will find any different result. Greenwald says Willet's study relied on the recall of participants, and there were "methodological and design problems," said Ernst Wynder, director of the American Health Foundation. "The totality of evidence, including a half century of animal model data, ecological data, the meta-analysis of 12 case–control studies, and plausible biological mechanisms which support the fat hypothesis" should be considered before drawing conclusions from this single study, said Wynder.

The NCI has launched a large trial to reconcile the positive correlations from international studies with the lack of positive findings from Willett's study and other case–control and cohort studies. But the $140-million, 15-year Women's Health Trial has provoked a storm of controversy because of concerns about the study's statistical power to detect an effect. Ross Prentice, head of the division of Public Health Sciences at the Fred Hutchinson Cancer Research Center in Seattle which is leading the Women's Health Trial, countered that the study is meant to answer "the public health question." Said Prentice, "The purpose is to identify a practical strategy for women to reduce their risk of cancer and other common diseases through dietary modifications that the general public can adhere to. . . . It is much less important to know exactly which change caused what degree of risk reduction, although it is of intellectual interest."

What about the contribution of food nutrients, particularly antioxidant vitamins E and C and beta-carotene (vitamin A) in reducing the risk of developing breast cancer, and indeed any cancer? Results from a 1993 study in China showed that people who took vitamins A and E had a 13% lower risk of dying from cancer and raised hopes that disease prevention was as close as a multivitamin. But, that same year, Willett reported that large intakes of vitamin C or E didn't protect against breast cancer. He did, however, observe a significant inverse association of vitamin A intake and breast cancer risk.

Colon cancer. There is perhaps a less ambiguous association between dietary fat and colon cancer, which, along with rectal cancer, is the most common form of cancer in the United States. Positive associations between animal (but not vegetable) fat consumption and colon cancer rates have been seen in many, but not all, studies. The question here has largely been which kind of fat is implicated. In the 1992 Harvard study of 89,000 nurses, those whose diets were high



Steve McCaw

A shift in the balance. Experiments on obese rats suggest weight may play a large role in cancer risk.

in red meat and animal fat were more likely to develop colon cancer than those who ate poultry and seafood. Another study of 49,000 men, published in 1992 by the Harvard School of Public Health, showed that those who ate a high-fat, low-fiber diet quadrupled their risk of developing precancerous colon polyps. But in this study, the risk was said to be due to the consumption of saturated fat (corn oil or corn/safflower oil), rather than polyunsaturated or monounsaturated fat intake (coconut oil, olive oil, marine fish oil). A further analysis of the same data earlier this year found that men with a high alcohol intake and a diet low in fruits, vegetables, and whole-grain foods are particularly vulnerable to colon cancer.

A review of the epidemiological literature concerning the contribution of fat, fiber, and calories to colon cancer by Bandaru Reddy, a researcher in the division of nutritional carcinogenesis at the American Health Foundation, found that most epidemiological models suggest that fat intake may be even more important than calorie intake in colon carcinogenesis. "However, the literature remains confusing, although the majority of these researchers agree that diets low in fat, high in dietary fibers, and high in fruits, vegetables, and calcium content are inversely associated with colon cancer risk," Reddy wrote in the journal *Preventive Medicine* in 1993.

Because many studies of fiber have shown a protective effect against colon cancer, the question arises whether it is fiber or fat that is a primary risk factor for colon cancer. Johanna Dwyer, a Tufts University cancer researcher, says, "I think it is both fat and fiber, but researchers generally fall into one camp or another."

To answer the question, the NCI is undertaking the Multisite Polyp Prevention Study to study the effect of decreasing dietary fat intake and increasing dietary fiber intake, both which can be achieved through eating more fruits and vegetables. The randomized, controlled study is based on the assumption that because there is a strong association between colon polyps and the development of colon cancer, an intervention that reduces the recurrence of large-bowel polyps has a strong likelihood of reducing the incidence of large-bowel cancer. The study is being conducted at 10 academic medical centers across the United States and is enrolling 2,000 male and female colon cancer patients over the age of 35. Half of the patients will be randomized to a control group with no intervention except for information on basic nutrition, and the other half will be assigned to the diet intervention group with target goals of eating 20% of calories from fat, 18 grams of fiber per 1,000 calories and 5–8 servings of fruits and vegetables daily. The recurrence of polyps in both groups at the end of years one and four will determine the effectiveness of dietary intervention. Initial results from an Australian Polyp Prevention Project of 400 colon cancer patients show no difference in the incidence of new cancers in a group randomized to a low-fat diet, but do show a trend for reduction of cancer spread in the group randomized to a high-fiber diet, according to Reddy.

Meaningful Mechanisms

If human studies can't answer the question, can laboratory experiments? Some researchers believe the mechanisms by which fat affects cancer risk have been neatly worked out, while some argue that most animal nutritional experiments have no relevance to humans because the animals are generally obese, thus skewing the contribution of calories to carcinogenesis.

David Rose, associate director of the American Health Foundation, has conducted numerous animal studies that he says show fat can be associated with cancer in two ways. According to one theory, fat intake can change specific fatty acids on the cell membrane, altering their function and the production of prostaglandins, which can then suppress the functioning of the immune system. High-fat diets and omega-6 polyunsaturated fatty acids, such as corn oils, have these effects, but omega-3 fatty acids, such as fish oil, do not, Rose says.

The second mechanism involves the way the body handles estrogen. One of the least controversial notions about breast cancer is "that estrogen plays some sort of promotional role," Rose asserts. Dietary fat can alter the production, metabolism, and excretion of estrogen. High-fat diets alter the type of bacteria and enzymes found in the intestinal tract, leading to an increased capacity to break down estrogen, allowing more estrogen to be reabsorbed into the body. "It [estrogen] may not initiate the tumor, although some people think that's possible, but it helps the cancer develop," says Rose. "High fiber in a diet has the reverse effect by decreasing the ability of estrogen to be reabsorbed."

This "gut story" may play a role in many cancers, including colon and prostate cancer, Rose says. While estrogen may not be involved in these other cancers, the ability of the intestinal tract to eliminate potential carcinogens is.

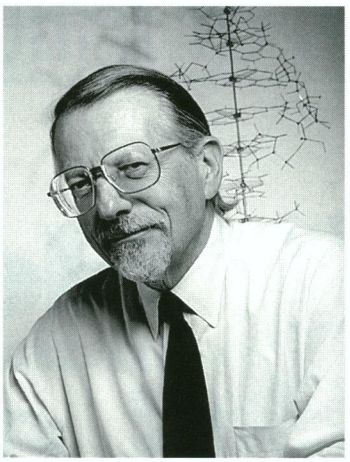
Willett believes estrogen may be important, but not specifically for the reasons Rose cites. He believes elevated levels of estrogen cause women to menstruate earlier, and therefore heightens the degree to which estrogen is active. Observational studies have shown that early menarche is associated with earlier onset of breast cancer. Willett also postulates that "energy restrictions" or low caloric intake in early life could confer a protective effect on breast cancer, whether or not the energy is derived from fat or calories. He notes a high association between tall women and breast cancer, saying that rapid growth in youth may set in motion the wheels of uncontrolled cancerous cell division. "Energy restriction during growth has emerged as a promising hypothesis which may explain much of the international variability—but it doesn't suggest a feasible intervention," Willett says.

Studies on the role of calories in breast cancer have centered on body mass because caloric intake contributes to obesity. But

study findings have been puzzling, according to Louise Brinton, of the NCI's Environmental Epidemiology Branch. Although increased body mass has now been fairly consistently shown to increase the risk of the development of postmenopausal breast cancer, "there has been a surprising lack of attention on weight loss as an intervention for lowering breast cancer risk," she says.

But here animal studies may provide some insights. Like a growing number of scientists who study diet and cancer in laboratory animals, Angelo Turturo of the Division of Biometry and Risk Assessment at the FDA's National Center for Toxicological Research believes control of calories is the key to many types of cancer. "Just as an effect of calorie restriction, live tumor incidence in lab animals can go from zero to seventy percent. You can shut it off with low calorie intake." When baby mice are given doses of a carcinogen and high calories, "they can get a liver tumor at one year," Turturo says. "But calorie restrict other mice at four months who are also receiving the same carcinogen and they won't get cancer."

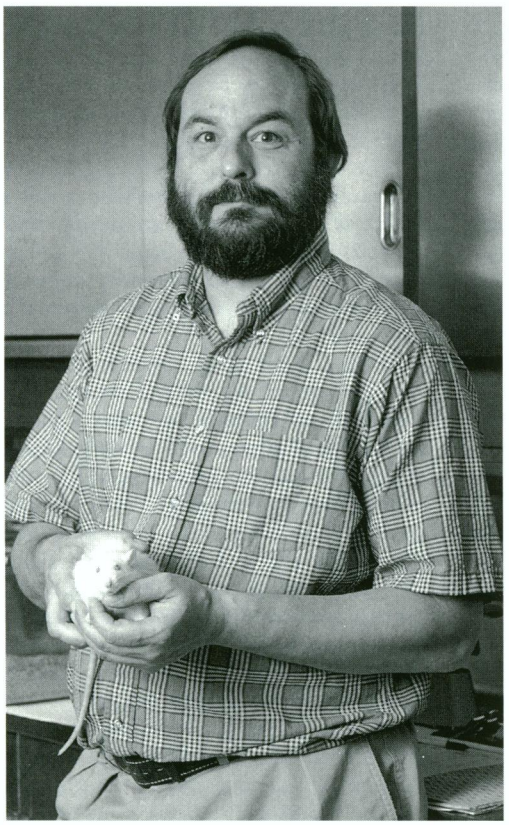
According to Turturo, tumorigenesis is often the result of a promotional effect on endogenous hormones and the stimulation of growth factors. The job of the endocrine system is to regulate growth and the development of organs based on available energy and physiology. "The question is not if calories promote cancer, but why wouldn't they promote cancer?" he says. "Some people have the bizarre notion that normal growth and carcinogenesis are not related. Calorie restriction can affect physiological, cellular, biochemical, and such molecular processes as endocrine homeostatsis, promotion, oncogene expression, progression and the immune response, which affect all steps in the induction of toxicity." Turturo says that most epidemiological studies are "useless" and all interventional studies have failed because they rarely control for calorie intake. "We've known since the 1930s that calorie intake can significantly affect life span and that the most efficient modulator of cancer is total calories."



Columbia Presbyterian Cancer Ctr.

Bernard Weinstein—We need to develop dietary biomarkers.

Animal experimentation can answer questions about cancer risk, but not if the animals are obese—as most are, maintains Frank Kari, a nutritionist at the NIEHS. Kari has found that some chemicals shown to be carcinogenic in these overweight animals do not produce cancer in calorie-restricted animals. "I noticed over the last decade that the average weight of rats and mice was increasing. Most of these animals eat and drink as much as they want and consequently are obese. I also noticed a relationship between lesions and weight and found that the heavier animals tend to die spontaneously of a lot of different chronic diseases," said Kari.



Steve McCaw

Frank Kari—We may be setting ourselves up through diet to be at risk from potential carcinogens.

Kari designed a set of experiments, the results of which will be presented later this summer, that show that certain chemicals now regulated as carcinogens are not carcinogenic in rats and mice that are just 5–7% lighter than most laboratory animals. These chemicals include two commonly used pharmaceuticals, a food additive, and an industrial pollutant. "I found I could turn a carcinogen into a noncarcinogen just depending on how heavy the host is," said Kari. "What this means to me is that it calls into question how we now regulate chemicals. The big picture that we do not look at is the wide range of outcomes available in the host. It may mean we can set ourselves up nutritionally to be at risk to potential carcinogens."

Animal studies by the Health Protection Branch of National Health and Welfare in Ottawa, Canada, looked at the effects of dietary modifications on cell proliferation. They found that diet- and calorie-restricted mice showed less cell division in seven tissues, including the mammary gland, which was the most affected in nonrestricted animals. "If a cell doesn't proliferate, it doesn't produce a tumor," says biologist Eric Lok. On the other hand, Lok adds, when a cell divides at a high rate given excess calories and energy, there may be a greater chance a somatic mutation will occur, possibly as a result of environmental chemicals, and will become fixed in the genome.

But Lois Gold, a biochemist at the University of California-Berkeley, maintains that animal studies such as those by Lok cannot answer the specific question of which dietary nutrients promote which cancer. "In rodents, we never get more than a 50% chance that a tumor will occur in the same site twice in these studies," she said. "All we are finding is that obese rats have more cell division." Weinstein disagrees with Gold's assertion that animal studies have little value. "Gold underrates the predictive value of the assays. There is a unity of biology across rats and humans that tells us valuable things. Dose responses may be a problem, but if you abandon them, you are left with nothing." What the field needs now is "more objective markers of the action in the body of what we eat. We have made too many inferences and associations," Weinstein says. "We need to take our cue from cardiovascular disease studies that routinely measure serum cholesterol, HDL, LDL, and other markers. We just cannot stay in the old rut of dietary history. We need to know what is happening in tissues, in DNA." Weinstein says that although such biomarkers will be expensive to develop, widespread use of them in interventional studies will reduce costs.

"We are at an exciting point where the revolution in our knowledge of the cellular and molecular basis of cancer can start to be applied with nutritional studies," Weinstein continues. "And we need to double our efforts because the public is already deciding what to do, in the absence of proof from us."

Renee Twombly

Renee Twombly is a freelance journalist in Durham, North Carolina.